CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20773

FINAL PRINTED LABELING

10/29/98

FDA DRAFT LABELING FOR NDA 20-773 (SonoRX)

(simethicone coated cellulose suspension, 7.5 mg/ml)

Bracco Diagnostics

Rx only

SonoRx[R]

Diagnostic ultrasound imaging agent

For oral administration only

DESCRIPTION:

*SonoRx (*simethicone coated cellulose suspension) is an orange-flavored, aqueous suspension, which consists of 22-micron cellulose fibers coated with 0.25% simethicone that is intended for oral administration.

Each ml of the suspension contains 7.5 mg of simethicone-coated cellulose.
Key ingredients are: xanthan gum, simethicone, and sodium lauryl sulfate.
Other ingredients are citric acid, fructose, orange oil, sodium benzoate, FD&C Yellow No. 6. and purified water.

CLINICAL PHARMACOLOGY

Pharmacodynamics: SonoRx when resuspended acts locally within the gastrointestinal tract to adsorb and disperse gas within the bowel lumen.

Pharmacokinetics:

The kinetics of SonoRx was evaluated in a vehicle control study of 10 normal volunteers (8 men and 2 women). Of these 10 volunteers, 7 (5 men and 2 women) received SonoRx (400 ml) and 3 (men) received the control (400 ml). The control agent was a formulation without simethicone coated cellulose, simethicone, xanthan gum and sodium lauryl sulfate. Silicon measurements in the blood and urine were monitored as the surrogate marker for simethicone. Silicon was measured over 5 days before dosing, and at 15, 30 minutes, 1, 2, 3, 6, 10, 15, 24 and 48 hours after dosing. In these subjects the concentrations of silicon detected in the blood (6.04 - 7.47 ug/ml) in 2 of the SonoRx treated subjects before SonoRx were similar to those detected in the blood after SonoRx (5.61 - 11.42 ug/ml).

The other 5 SonoRx treated subjects did not have silicon detected in the blood before SonoRx, and 2 of the 5 had levels of silicon detected after SonoRx; however, these levels were similar to those of the subjects who had silicon detected in the blood before and after SonoRx. Urine levels of silicon in all subjects were similar before and after SonoRx. The silicon levels in the blood and urine before and after the control were similar to those before and after SonoRx.

Elimination: The cellulose component of SonoRx is eliminated in the feces.

Metabolism: Metabolic studies of simethicone coated cellulose were not conducted. Cellulose is known not be metabolized by humans.

Protein Binding: Plasma protein binding and gastrointestinal protein binding were not studied.

Food Effects: Food effects studies were not conducted.

Gender Effects: The effects of gender on the pharmacokinetics of SonoRx were not studied.

Pediatrics: Pharmacokinetic studies in pediatric patients were not conducted.

Geriatrics: Pharmacokinetic studies in geriatric patients were not conducted.

Special Populations: The pharmacokinetics and rate of fecal elimination was studied in 15 patients with impaired bowel motility or impaired bowel mucosa. The trial design was similar to that described in the preceding pharmacokinetics section. Of these patients, 12 received SonoRx and 3 received the vehicle. In these patients the detection of silicon, as a surrogate market for simethicone, in the blood and urine was similar to that of the normal volunteers reported in the preceding pharmacokinetics section.

As in the normal volunteers, the cellulose component of SonoRx was eliminated in feces. Based on the fraction of ingested fiber that was eliminated in feces following the administration of SonoRx, the rate of fecal elimination of cellulose appears to be lower in these patients with impaired bowel motility or impaired bowel mucosa than in the normal volunteers.

Dose Response Studies: Based upon preliminary studies of various doses, 400 ml of SonoRx was selected for additional study. The benefit of higher doses was not confirmed in larger clinical studies. As with other large volumes of orally ingested products, patient compliance decreased with increasing volumes. (See Precautions Section).

Drug-Drug Interactions: Drug interaction studies have not been conducted with SonoRx to determine the effect of SonoRx on the absorption of other drugs.

CLINICAL TRIALS

In 3 controlled clinical studies to evaluate the potential benefits of SonoRx, 292 persons were enrolled (including 53 patients in a cross over study); of these, 238 patients received SonoRx and 105 received a control agent. The racial distribution of the SonoRx treated patients is 78% White, 18.2% Black, 2.4% Hispanic, 0.7% Asian, and 0.3% other racial or ethnic groups. Of the 292 patients (138 women; 154 men), the mean age is 55 (range 22 to 89) years.

Of the 292 patients, a total of 239 patients were evaluated in two clinical studies (117 in Study A; 122 in Study B) in which the patients received either 400 ml of SonoRx (93 patients in study A; 94 patients in study B), or received 400 ml of a control agent (24 patients in study A; 28 patients in study B). The control agent is a formulation without simethicone coated cellulose, simethicone, xanthan gum and sodium lauryl sulfate. All enrolled patients were highly suspected of having upper abdominal pathology and were referred for abdominal ultrasound imaging. Images before and after either SonoRx or the vehicle control were separated by 20 minutes.

In these two studies ultrasound images before and after SonoRx for each patient were evaluated in paired blinded readings by four radiologists. Two radiologists evaluated static images; two radiologist evaluated both static and video images. Before and after SonoRx the images were scored for the presence of gas shadowing artifacts (0 = completely obscured, 4 = not obscured); the delineation of anatomic organs was scored as 0 = none to 4 = excellent.

As shown in table 1, for the blinded readers with both static and video images in studies A and B, SonoRx images provided statistically significant improvement over baseline of at least one unit in the delineation of the stomach, gastric wall, pylorus, duodenum, and pancreas.

Table 1
PROPORTION OF PATIENTS WHOSE ANATOMIC DELINEATION IMPROVED AFTER SONORX (1)

Anatomic Area	Blinded Reader	Study A N(2) = 64	Study B N(2) = 81
Stomach	a	47 (73%)	65 (80%)
	b	41 (64%)	60 (74%)
Gastric Wall	a	46 (72%)	62 (77%)
	b	37 (58%)	65 (80%)
Pylorus	a	44 (69%)	51 (63%)
	b	30 (47%)	54 (67%)
Duodenum	a	43 (67%)	45 (57%)
	b	28 (44%)	42 (52%)
Pancreatic Head	a	11 (17%)	44 (54%)
	b	25 (39%)	16 (20%)
Pancreatic Body	a	8 (13%)	37 (46%)
	b	16 (25%)	11 (14%)
Pancreatic Tail	a	29 (45%)	43 (53%)
	b	19 (30%)	25 (31%)

(1) Depending upon the reader and the anatomic site, 0-10 patients in study A and 0-2 patients in Study B had more delineation before SonoRx.
(2) N is the number of patients considered in the analysis. Because of protocol violations, 29 SonoRx treated patients in Study A; 13 patients in Study B were not included.

For all SonoRx treated patients in study B, all 4 blinded readers reported less gas shadowing artifact on the SonoRx images in 20 (21%) to 54 (57%) of images depending upon the blinded reader. For all SonoRx treated patients in study A, of the 4 blinded readers, the two readers with static images only reported less gas shadowing artifact with SonoRx in 27 (29%) of patients. For the two blinded readers with static and video images, one reader reported less gas shadowing artifact after SonoRx, and one reader reported less gas shadowing artifact on the pre images.

The clinical studies were not designed to confirm the presence or type of pathology.

INDICATION

SonoRx is an orally administered gas shadowing reduction agent that is indicated to enhance the delineation of upper abdominal anatomy in conjunction with ultrasound imaging.

SonoRx is not indicated as a therapeutic antiflatulence or gastrointestinal motility agent.

CONTRAINDICATION

As with other large volume oral contrast agents, SonoRx is contraindicated in patients with known or suspected intestinal perforation and obstruction. (See Warnings section regarding potential intraperitoneal inflammation and cellulose accumulation) .

SonoRx is contraindicated in patients with known allergy to its active or inactive ingredients.

WARNINGS

The ingestion of SonoRx may cause vomiting that could be associated with aspiration. Of the 385 patients or normal volunteers who received SonoRx, nausea was reported in 13 (3.4%) and vomiting in 8 (2.1%). Also, patients who have a tracheosophageal fistula may aspirate. Precautions should be taken to avoid aspiration.

The effects of SonoRx on human peritoneal tissues have not been studied. In rats, throughout a 3 month study observation period, after the intraperitoneal injection of SonoRx at the lowest test dose of 5 ml/kg, capsular granulomatous inflammation of the spleen, liver and kidneys, and apparent accumulation of cellulose in the red pulp of the spleen and glomeruli of the kidneys were observed. The effects of SonoRx on human peritoneal tissues are not known.

PRECAUTIONS

General

SonoRx is associated with nausea, vomiting and abdominal pain. In patients who have these symptoms before the ingestion of SonoRx, the symptoms could increase in severity. This could confound the ability to distinguish adverse effects of SonoRx from the signs and symptoms of obstruction or perforation , and from any pre-existing conditions.

Patients who have a current or recent history of hiatal hernia, esophageal reflux, nausea, vomiting or abdominal pain may not be able to tolerate SonoRx. Studies have not been conducted in these patients.

SonoRx should be given with caution to patients who cannot tolerate large fluid shifts and who are on specific fluid intake requirements.

Information for Patients

Patients who are candidates to receive *SonoRx* should be instructed to inform the physician if they are pregnant or breast feeding.

Patients should be informed of the following:

SonoRx is prescribed for delineation of abdominal anatomy during ultrasound imaging

1. SonoRx can cause nausea, vomiting, diarrhea, abdominal pain, or other gastro-intestinal discomfort.
2. For most patients complete elimination of *SonoRx* occurs within 24 to 48 hours following administration
3 Feces may appear orange-colored until *SonoRx* is completely eliminated.

Patients should be asked if they are able to drink, approximately 400 ml (approximately 14 ounces or 1 pint) over a 15 minute period. Patients should be asked if they have a hiatal hernia, or problems with regurgitation when they lie on their backs after eating.

Drug/Laboratory Test Interactions

None known

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted to evaluate the carcinogenic potential of *SonoRx*.

The results of the following genotoxicity studies with SonoRx were negative: 1) Salmonella-Escherichia coli reverse mutation assay, 2) mammalian chromosome aberration assay using Chinese hamster ovary (CHO) cells, 3) CHO/HGPRT forward mutation assay, and 4) mouse micronucleus assay.

No effects on male or female fertility or reproductive capacity were exhibited by rats orally administered SonoRx at doses up to 40 ml/kg/day (approximately the recommended single human dose based on body surface area).

Pregnancy

Pregnancy category B.

A developmental toxicity study was performed in rabbits at doses during organogenesis up to 10 ml/kg/day(approximately one half of the single recommended human dose based on body surface area). No evidence of maternal toxicity or fetal harm due to SonoRx was noted. However, adequate and well-controlled clinical studies have not been conducted in pregnant women. Since animal reproduction studies are not always predictive of human response, SonoRx should be used in pregnancy only if essential.

Nursing Mothers
Studies have not been conducted to determine whether SonoRx is excreted in human milk.

Because many drugs are excreted in human milk, caution should be exercised when SonoRx is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of *SonoRx* in children have not been established. Dose adjustments for the capacity of the upper gastrointestinal tract have not been studied.

ADVERSE EVENTS

SonoRx was evaluated in clinical trials involving 448 subjects (406 patients and 42 normal volunteers). The overall racial and ethnic representation is 75% Caucasian, 20% Black, 4% Hispanic, 1% Asian, and <1% other. Of the 448 subjects there were 260 men, 188 women with a mean age of 52 (range 18 to 89). Of the 448 subjects, 385 received SonoRx, 138 received a control agent, and 75 received both in cross over studies.

Of the 448 subjects evaluated, 68/385 (18%) who received SonoRx and 16/138 (12%) patients who received a control agent reported at least one adverse event. Of the subjects who received SonoRx, at least one adverse event was reported in 65 (19%) patients and 3 (8%) normal volunteers. Deaths or serious adverse events were not reported during the study observation period.

The most frequently reported adverse events were associated with the digestive system. Diarrhea was reported in 21 (5.5%), nausea in 13 (3.4%), vomiting in 8 (2.1%) of subjects who received SonoRx. Orange colored stools may occur. Events which occurred in the total population (volunteers and patients) receiving *SonoRx* at a frequency of ≥ 0.5% are listed by body system in Table 2.

Table 2
ADVERSE EVENTS REPORTS in ≥ 0.5% of SUBJECTS WHO RECEIVED SONORX in CLINICAL TRIALS.

Body System	Event	SonoRx Control n=385	Control Agent n=138
Body as a Whole		25 (6.5%)	6 (4.3%)
	Abdominal Pain	8 (2.1%)	1 (0.7%)
	Headache	7 (1.8%)	1 (0.7%)
	Back pain	4 (1.0%)	1 (0.7%)
	Chest pain	3 (0.8%)	1 (0.7%)
	Chills	2 (0.5%)	0
Digestive		45 (11.7%)	9 (6.5%)
	Diarrhea	21 (5.5%)	4 (2.9%)
	Nausea	13 (3.4%)	1 (0.7%)
	Vomiting	8 (2.1%)	0
	Eructation	4 (1.0%)	1 (0.7%)
	Dyspepsia	2 (0.5%)	2 (1.4%)
	Flatulence	2 (0.5%)	0
Respiratory		7 (1,8%)	0
	Pharyngitis	2 (0.5%)	0
	Rhinitis	2 (0.5%)	0
Skin & Appendages		2 (0.5%)	0
	Rash	2 (0.5%)	0
Special Senses		3 (0.8%)	0
	Ear Pain	2 (0.5%)	0

The following additional adverse events (listed by body system) were reported in less than 0.5% of persons who received SonoRx.

Body as a whole: asthenia, fever, malaise, neck pain, pelvic pain, pain
Cardiovascular: bradycardia, hematoma, hypertension, pallor, palpitations, tachycardia
Digestive: dysphagia, dry mouth, melena
Hemic/Lymphatic: ecchymosis, lymphadenopathy
Metabolic/Nutritional: hypoglycemia
Nervous: hypertonia, somnolence
Respiratory: epistaxis, pneumothorax, sinusitis
Urogenital: dysuria

OVERDOSAGE

Overdose information with *SonoRx* has not been reported.

DOSAGE AND ADMINISTRATION

The recommended dose of *SonoRx* is 400 ml administered orally over 15 minutes. SonoRx should be taken after fasting for at least 4 hours.

Imaging: Abdominal ultrasound imaging should begin within 10 minutes after completing the ingestion of SonoRx.

Drug Preparation

Prior to administration, the container of *SonoRx* should be inverted and shaken vigorously to resuspend any material that has settled. The suspension should stand unopened for 2 minutes before administration to the patient to allow excess air to escape.

How Supplied

SonoRx is supplied in clear glass bottles containing a 400 ml single dose.

Storage

Store at controlled room temperature 20-25^0 C (68-77^0 F) [see USP]. Do not freeze.

Manufactured for
Bracco Diagnostics Inc.
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By

Westwood Squibb™
A Bristol-Myers Squibb Company
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Under License from ImaRx Pharmaceutical Corp.

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